THE EXPERT ADVISORY COMMITTEE ON DRUGS (EACD) ADVICE
TO THE MINISTER ON:

BENZYLPIPERAZINE (BZP)

April 2004
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EXECUTIVE SUMMARY

The Expert Advisory Committee on Drugs (EACD) considered benzylpiperazine (BZP) and related substances at its meeting of 19 March 2004. The EACD considered evidence provided by the Ministry of Health’s secretariat, the New Zealand drug enforcement agencies and others. The EACD considered the information before it in the terms of the criteria the EACD must apply before making a recommendation to the Minister. It concluded that there was insufficient information available on which to base a recommendation to classify these substances in the schedules of the Misuse of Drugs Act 1975. However, the EACD brings to your attention some matters the committee members considered important and which, if acted on, may form the basis for reconsideration by the EACD.

The Committee considers that:

- more information on the health effects of BZP and similar substances should be obtained
- The prevalence of BZP use should be investigated, possibly through routine toxicological screening through community laboratories.
- It is inappropriate for BZP to be marketed as a dietary supplement.
- Regulatory options should be explored which could provide additional classifications in the Act allowing partial control, eg putting conditions on the promotion or sale of products, particularly to young people.
- There is reason to be concerned that evidence indicates that BZP can create adverse reactions when taken with prescription medicines, such as Selective Serotonin Re-uptake Inhibitors (SSRI’s).
- Restricting access to the products that contain BZP may lead to users of these products seeking more harmful controlled drugs as substitutes for BZP.
- Papers provided to the Committee included proposed moves by the industry to develop “self-regulation” covering issues such as advertising, age-of-use, labelling and retailing. The EACD is not recommending industry self-regulation as the preferred long-term regulatory option.

This paper presents evidence on the risk of harm associated with Benzylpiperazine (BZP) and similar substances. They are stimulant type substances that produce effects similar to known amphetamines and hallucinogens. The information presented addresses the criteria that the Expert Advisory Committee on Drugs (EACD), must take account of when considering the appropriate classification of a substance under section 4B of the Act.
There is some concern over the increase in supply of these products, which are marketed and distributed independently over the internet, through counter-culture retailers, and more recently in liquor outlets, service stations and dairies. Advertising of these products has occurred in a manner that appears to take no account of the impact on younger people. A significant industry has developed, with at least 1.5 million doses having been manufactured in New Zealand last year.

The base substance benzylpiperazine (BZP) has legitimate therapeutic uses as a treatment for internal parasites in cattle. Although it has been clinically trialled in some countries as an antidepressant medication for humans, there is no known human therapeutic use of BZP.

**Recommendations**

After considering all of the information put to the Committee and the classification criteria in the Misuse of Drugs Act 1975, the EACD makes the following recommendations to the Associate Minister of Health:

(a) After considering the evidence the EACD believes that there is no current schedule of the Misuse of Drugs Act 1975 under which BZP could reasonably be placed.

(b) The Minister of Food Safety should be requested to consider the appropriateness of permitting the chemical, BZP to be sold as a dietary supplement in New Zealand when it has no known nutritional value.

(c) The EACD recommends that the Minister direct the Ministry of Health to conduct further research into the potential harms associated with the use of BZP.

(d) The EACD recommends that the Minister direct the Ministry of Health to investigate the possibility of gathering prevalence data on BZP via the introduction of routine toxicology screening via community laboratories.

(e) The EACD recommends that the Minister direct the Ministry of Health to examine options for new categories of classification that can incorporate some levels of control and regulation, such as an 18 plus age limit, without prohibiting access to these substances completely.

(f) This paper should be made publicly available (eg, posted on the National Drug Policy website www.ndp.govt.nz) as soon as practicable.

(g) All media queries relating to this report should be referred to the Ministry of Health Communications Team.
Substance identification

Piperazines are stimulant type substance, derived from the pepper plant or by synthetic reproduction (RADS, 2003). BZP is known to bind with the serotonin receptors (D. de Boer et al, 2001), though not selectively. BZP was originally synthesised as a potential antihelminthic agent (a treatment for internal parasites), however it was subsequently found to reverse the effects of tetrabenazine in rats and mice, indicating potential antidepressant activity of clinical importance (Miller et al, 1971). Subsequent studies indicated that the compound had a similar type of action to dexamphetamine (H. Campbell et al, 1973).

Similarity to Known Substances

BZP has a reported similarity to dexamphetamine and when used in combination with trifluorophenylmethylpiperazine (TFMPP) has a reported effect similar to ecstasy (MDMA) (Bedford, 2001). Although BZP is known to have a similarity of action to dexamphetamine, it is considered to be approximately ten percent of the potency.

It is unlikely that users would attempt to match the dose strength of d-amphetamine as unwanted and unpleasant side effects are experienced at about 2 ½ times the average dose. (Average. dose = 100 mgs BZP) The duration of action for a 100mg dose is 6 – 8 hours.

Current Classification under the Act2

Neither BZP nor TFMPP are currently classified under the Act. They are being sold as dietary supplements, however, New Zealand Food Safety Authority is considering expert advice that BZP does not meet the criteria for dietary supplements.

Rationale for Classification2

Likelihood or evidence of drug abuse

Many reports of recreational use of BZP & TFMPP are available and evidence exists that they are being marketed as a ‘legal’ alternative to illicit substances of similar effect. It is likely they will be used and misused in a similar manner to other recreational substances. The Community Alcohol & Drug Services report that these substances are being recorded as part of the drug use repertoire of clients assessed for drug related harm, though there are no presentations for problems specifically with the piperazines. These substances may be used in the context of poly drug use, therefore synergies with other substances will be an influence on whether the

2 Section 4B(2) sets out the matters which the Minister of Health must have regard to, and to which the EACD must give advice on, when considering a particular drug. Information on each criterion should be submitted.
substance is used safely or abused. BZP is being taken regularly by many people, often as a substitute for illicit drugs, but frequently in combination with them, usually to promote wakefulness and to ameliorate the depressant effects of alcohol and/or cannabis.

**Specific effects of the drug**

BZP and TFMPP are central nervous system (CNS) stimulants. For BZP, doses of 20 to 100mgs produce euphoria, wakefulness and increased vigilance. The duration of action is 6 to 8 hours (Erowid, 1997). A combination of BZP and TFMPP is reported to produce effects similar to MDMA (Bedford, 2001), a substance that is sometimes referred to as an “entactogen”, (meaning ‘to touch within), (Nichols, 1996). Dehydration may be associated with BZP therefore risks of over re-hydration may be present. This effect is not discussed in the literature. However, anecdotes from the community suggest that it can be problematic if used in conjunction with alcohol. The duration of action for a 100mg dose is 6 – 8 hours. However, information from one user/distributor suggests that if 500mgs is taken, then wakefulness can last up to 48 hrs, however such a dose is likely to also cause nausea.

**Potential to cause death**

One case study has been reported) in which a 23 year old woman died 68 hours after ingesting BZP and 64 hours post ingestion of MDMA and a large volume of water (Balmelli C. et al. 2001. No linkage with the BZP was made and the death displayed all the characteristics of an ecstasy related death. She was diagnosed with cerebral oedema and with beginning tonsillar herniation.

This case, was considered by the United States federal authorities (DEA) as evidence of BZPs potential to cause death (even though no causal links were established, the substance was implicated by its presence), and led to BZP being placed in schedule 1 in 2002.

Other than this one case, no other fatalities are known of, therefore BZPs known potential to cause death is low, or as yet unknown.

**Risks to public health**

Use of piperazines may have the potential to start a pattern of abuse or lead to the use of more powerful illicit substances of a similar kind. Conversely, their use can reverse an abusive pattern and help avoid more powerful and harmful substances. At present, these substances are cheaper than similar illicits, with the price being set by the market, at a level related to the cost of illicits, undercutting them by 50%. Approximately 1.5 to 2 million tablets have been manufactured by Vitafit Nutrition Ltd. for Stargate International (one of the major distributors in New Zealand) since 2001 (MOH, 2003).

Piperazine users conditioned to the effects of stimulants may more readily transfer to harmful illicit street drugs. However, there is no reported criminal behaviour associated with the use of BZP & TFMPP, as they are moderately priced and have a lower dependence potential than illicit amphetamines.
They are retailed mainly within counter-culture venues, which do not have restrictions on opening hours, other than self-imposed limits. One retailer is known to have 24-hour availability, through the operation of a manned vending window. There are recent reports of sale at liquor outlets, service stations and convenience stores. There is no restriction on the type or style of advertising for the commercial products containing piperazines that they distribute. All suppliers avoid making therapeutic claims as they do not want their products to be subject to the controls contained in the Medicines Act 1981. These products are often marketed as if they were just another recreational substance or as a substitute for other drugs, with the advantage of being legal. There is no age restriction on purchasers, therefore the discretion of the retailer prevails.

**Therapeutic value**

There are no current therapeutic uses of BZP or similar substances in humans. It is not known whether they may have any future use in substitution treatment for dependent amphetamine or methamphetamine users. It has been suggested that they may be able to be used as a non-injectable, oral alternative to illicit stimulants as a harm reduction strategy for continuing users.

BZP has been trialled as an antidepressant, though never marketed. BZP has in the past been an active ingredient in worming tablets and continues to be used for this purpose in agriculture. A legitimate supply will continue to remain available in New Zealand for this purpose.

**Ability to create physical or psychological dependence**

No evidence of physical dependence has been described with the substances being used orally. There is no reference to the injecting route being favoured. Development of tolerance may occur, but higher doses are associated with increased unwanted side effects. There is some possibility for a mild psychological dependence to develop due to repeated self administration and the subsequent reliance upon the subjective effects to overcome inhibitions or to give the energy/wakefulness required to participate in the social environment, particularly within the urban dance environment.

**International classification and experience**

The United States DEA classified BZP and TFMPP in Schedule 1 by emergency order on September 20, 2002, following the reported death of a 23 year old woman who had also taken MDMA several hours following ingestion of BZP. Some states in Australia have also scheduled BZP.
Other Relevant Information

There has been an increase in the availability of non-traditional ‘designer’ substances that give similar effects to known CNS stimulants and hallucinogens. They have been distributed through internet networks and counter-culture retailers associated with “dance” culture as legal alternatives to the illicit drugs for which they are either substitutes or additives.

This has created a concern about their potential for harm to the public health and about the possible responses to their use and/or abuse. Because there are many new substances that could appear on the market in this way, the challenge for public health practitioners and regulators is how to respond to these new substances in a way that promotes the public health while protecting individual rights. They are generally of lower potency and price than of illicit amphetamines and methamphetamine, and they are commercially packaged, labelled with the major ingredients and their strengths. The distributors would argue that this is a responsible approach to a demonstrated demand for the effects given by these substances.

When first distributed, this was an approach that allowed users to exit the illicit market with its inherent risks and the often poor quality drugs. Substitution of illicit with piperazines is occurring, mostly amongst users who are afraid of the damage to their lives that a conviction would bring and who also wish to normalise the transaction required to purchase their choice of recreational substance. However, being unregulated at this time, they are being promoted within the free market, which has the generation of profit as the driving force. This can as easily lead to market saturation as can the imperatives driving the black market.

Unlike either novel foods or new medicines, these products are being marketed without adequate scientific safety assessments because there is no need for the distributor to seek regulatory pre-market approval from a regulatory agency.

Possible Industry Self-Regulation

Ministry of Health officials have met with the industry. Discussion of the reasons behind the importation of BZP and other like products took place. They commented that there was increasing dissatisfaction with the quality of the illicit substances used by the ‘dance’ community, that many maturing users no longer feeling comfortable accessing their needs illegally, as they risked their employment, arrest and their health from harder drug use – such as methamphetamine.

The Ministry of Health told them of concerns relating to the marketing of these substances, as there has been some promotion on radio that fell below reasonable standards (i.e., content designed to appeal to youth), sale through inappropriate outlets (e.g., service stations, dairies), and unsatisfactory labelling of some of these substances, (eg ingredient list and their strengths).

The industry proposed that they would make contact with other distributors and discuss the issues with them, with the view to forming a trade group to administer rules that would govern advertising, age of use, labelling and retailing.
Papers provided to the committee included proposed moves by the industry to develop “self-regulation” covering issues such as advertising, age-of-use, labelling and retailing. The EACD is not recommending industry self-regulation as the preferred long-term regulatory option.
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